

CORRESPONDENCE

Implications of Interleukin-6 (IL-6)-blockade for severe COVID-19 infection in patients with Multiple Myeloma

Nicola Sgberza, Paola Curci, Vanda Strafella, Rita Rizzi, Pellegrino Musto

Hematology and Bone Marrow Transplantation Unit - AOUC Policlinico, Department of Emergency and Organ Transplantation, "Aldo Moro" University, Bari, Italy

Cancer patients are at a higher risk of "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)" infection than patients without cancer (1). In particular, Multiple Myeloma (MM) patients are at serious risk of contracting this severe infection because of many factors, such as immunosuppression, comorbidities, immune deregulation and frequent accesses to hospital. At present, there are no proven agents for treatment or prevention of SARS-COV-2 infection, so single or combined therapeutic approaches repurposing existing anti-viral and anti-inflammatory drugs are currently utilized to treat patients with moderate to severe "Coronavirus Disease 2019" (COVID-19) infection. Among these, IL-6 inhibitors seem to be promising for the management of the massive cytokine storm associated with the development of the typical lung damage and consequent acute respiratory distress syndrome occurring in the most aggressive patterns of SARS-COV-2 infection (2-4). While different reports have been published about concomitant MM and COVID-19 infection, few data are available about the specific outcome of MM patients treated with IL-6 inhibitors. Available IL-6 inhibitors are siltuximab, tocilizumab and sarilumab. Siltuximab binds directly to IL-6, while tocilizumab and sarilumab target its soluble (sIL-6R) and membrane-bound receptors (mIL-6R). To our knowledge, from literature review, including case reports and case series, 49 patients (Table 1), with severe confirmed COVID-19 and MM, were treated with IL-6 inhibitors.

The most used IL-6 inhibitor was tocilizumab, FDA approved for the management of CAR T-cell related Cytokine Release Syndrome (CRS) while no patient was reported treated with siltuximab. Clinical outcome (alive/deceased) is available for 40 on 49 patients with questionable results: 20 patients (50%) died, 20 patients (50%) survived. Certainly, although this retrospective review includes a quite large cohort of patients (556), providing interesting information, several limitations to generalizability of findings are present. First, the number of patients with MM and COVID-19 infection treated with IL-6 inhibitors in

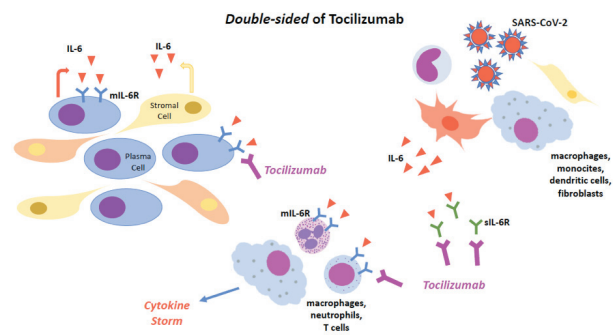


Figure 1. Double-sided of Tocilizumab. Interleukin-6 (IL-6) promotes the growth of human myeloma cells via autocrine and paracrine mechanisms; tocilizumab, binding to mIL-6R of myeloma cells, inhibits in vitro their proliferation. SARS-CoV-2 infection would cause the release of IL-6 by immune cells, with the development of cytokine storm (CS) mediated by macrophages, neutrophils and T cells; tocilizumab, binding to mIL-6R and sIL-6R, plays an important role in the treatment of CS induced by SARS-CoV-2.

Table 1. Summary of studies of IL-6 inhibitors for COVID-19 infection in patients with multiple myeloma.

Study Type	Country (total number of MM patients)	IL-6 inhibitor	Number of patients	Outcome		Reference
				Patients Deceased [20]	Patients Alive [20]	
Case series	Spain (167)	N.S.	22	15	7	Martínez-López J. et al. Multiple myeloma and SARS-CoV-2 infection: clinical characteristics and prognostic factors of inpatient mortality. <i>Blood Cancer J.</i> 2020 Oct 19;10(10):103. doi: 10.1038/s41408-020-00372-5.
Case series	Italy (106)	Tocilizumab	2	1	1	Passamonti F. et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. <i>Lancet Haematol.</i> 2020 Oct;7(10):e737-e745. doi: 10.1016/S2352-3026(20)30251-9.
Case series	USA (100)	Tocilizumab/Sarilumab	9	N.A.	N.A.	Hultcrantz M. et al. medRxiv [Preprint]. 2020 Jun 11:2020.06.09.20126516. doi: 10.1101/2020.06.09.20126516. Update in: This article has been published with doi: 10.1158/2643-3230.
Case series	UK (75)	Tocilizumab	1	1	0	Cook G. et al. Real-world assessment of the clinical impact of symptomatic infection with severe acute respiratory syndrome coronavirus (COVID-19 disease) in patients with multiple myeloma receiving systemic anti-cancer therapy. <i>Br J Haematol.</i> 2020 Jul;190(2):e83-e86. doi: 10.1111/bjh.16874.
Case series	USA (58)	N.S.	4	2	2	Wang B. et al. <i>J Hematol Oncol.</i> 2020 Jul 14;13(1):94. doi: 10.1186/s13045-020-00934-x.
Case series	Germany (21)	Tocilizumab	1	0	1	Engelhardt M. et al. <i>Haematologica.</i> 2020 Dec 1;105(12):2872-2878. doi: 10.3324/haematol.2020.262758. PMID: 33256391; PMCID: PMC7116370.
Case series	France (10)	Tocilizumab	2	0	2	Malard F. et al. COVID-19 outcomes in patients with hematologic disease. <i>Bone Marrow Transplant.</i> 2020 Nov;55(11):2180-2184. doi: 10.1038/s41409-020-0931-4.
Case series	Qatar (6)	Tocilizumab	2	1	1	Elsabah H. et al. The Outcome of Six Patients with COVID-19 Infection and Multiple Myeloma. <i>Mediterr J Hematol Infect Dis.</i> 2020 Nov 1;12(1):e2020082. doi: 10.4084/MJHID.2020.082.
Case series	USA (5)	Tocilizumab	2	0	2	Manasanch EE. et al. SARS-CoV-2 in multiple myeloma: initial observation and management. <i>Leuk Lymphoma.</i> 2020 Nov;61(11):2763-2766. doi: 10.1080/10428194.2020.1780588.
Case series	China (5)	Tocilizumab	1	0	1	Sun C. et al. COVID-19 in patients with multiple myeloma: a cross-sectional survey from the most severely affected region in China. <i>Leuk Lymphoma.</i> 2020 Dec 3:1-4. doi: 10.1080/10428194.2020.1834098.
Case report	UK (2)	Tocilizumab	2	0	2	Chaidos A. et al. Interleukin 6-blockade treatment for severe COVID-19 in two patients with multiple myeloma. <i>Br J Haematol.</i> 2020 Jul;190(1):e9-e11. doi: 10.1111/bjh.16787. Epub 2020 May 18. PMID: 32369612.
Case report	China (1)	Tocilizumab	1	0	1	Zhang X. et al. <i>Blood Adv.</i> 2020 Apr 14;4(7):1307-1310. doi: 10.1182/bloodadvances.2020001907. PMID: 32243501; PMCID: PMC7160284.

Abbreviations: N.S.: not specified; N.A.: not available

the world, is certainly higher than one reported in case reports/case series. Second, data represent experiences of patients from different centers, treated differently in terms of drugs and according to their availability at different hospitals. Third, patients received also additional therapies for COVID-19 including hydroxychloroquine and anti-viral agents, so it is not possible to distinguish absolutely the efficacy of tocilizumab (or other IL-6 inhibitors) from other drugs. An interesting aspect to focus on is the potential use of tocilizumab against MM. IL-6 is the major growth factor of human myeloma cells through an autocrine or a paracrine mechanism and tocilizumab was reported to inhibit their proliferation *in vitro* (5) and to be effective in stabilizing serum monoclonal protein in patients with systemic diseases (i.e. rheumatological disorders) and concomitant MM (6). So, in the subset of active MM patients with severe COVID-19 infection, in whom other anti-myeloma treatments could be not administrable, the possibility that tocilizumab could represent a treatment option with a double action (Figure 1) against cytokine storm due to COVID-19 and MM itself would warrant to be verified.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Received: 25 February 2021

Accepted: 7 April 2021

Correspondence: Nicola Sgherza, MD, PhD

Hematology and Bone Marrow Transplantation Unit - AOUC Policlinico, Department of Emergency and Organ Transplantation, "Aldo Moro" University, 70124, Bari, Italy

Tel.: +390805594001

Fax: +390805428978

E-mail: nicolasgherza@libero.it